I. Remarks

Claims 1, 4, and 6-11 are currently pending.

Claims 2, 3, and 5 have been canceled without prejudice with this response.

Claims 1, 9, and 10 have been amended with this response. Claim 1 has been amended to contain the limitations previously found in original claims 2, 3, and 5. Accordingly, support for the amendments is found throughout the instant specification. Claims 9 and 10 have been amended to independent claims with the language previously found in original claim 1 from which they depended. Accordingly, support for the amendments is found throughout the instant specification. As such, these amendments do not add new matter. Applicants respectfully request their entry.

II. Claim rejections under 35 U.S.C. § 112

Claim 3 stands rejected under 35 U.S.C. § 112, second paragraph, as being allegedly indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In particular, there is allegedly insufficient antecedent basis for the limitation "said tissue specific promoter". Claim 3 has been canceled without prejudice with this response. Accordingly, this rejection is moot. Applicants respectfully request its withdrawal.

III. Claim rejections under 35 U.S.C. § 102

Claims 1-3, 6, and 11 stand rejected under 35 U.S.C. § 102(e) as being allegedly anticipated by Snyder et al. (US 2002/0155580). Applicants respectfully traverse. Claim 1 has been amended to require that the recombinant adeno-associated virus encoding a Factor VIII protein be operably linked to a liver-specific promoter comprising at least a portion of the transthyretin (TTR) gene promoter. Snyder et al. does not teach or disclose a liver-specific promoter comprising at least a portion of the transthyretin (TTR) gene promoter. As such, Snyder et al. cannot and does not anticipate the instant claims. Applicants respectfully request its withdrawal.

IV. Claim rejections under 35 U.S.C. § 103(a)

A) Claims 1, 3, and 5 stand rejected under 35 U.S.C. § 103(a) as being allegedly unpatentable over Snyder et al. (US 2002/0155580) taken with Simonet (U.S. Patent Serial No. 6,268,212). In particular, the Office has concluded that it would have been obvious to a person of ordinary skill in the art to make a composition comprising a recombinant AAV comprising a nucleotide sequence encoding a B-

domain deleted human Factor VIII protein operably linked to a liver specific promoter comprising a portion of the TTR gene promoter. Applicants respectfully traverse.

The Office has failed to provide an objective teaching or suggestion which would have motivated an artisan to combine the elements of the prior art to arrive at the specific combination of a B-domain deleted human Factor VIII protein operably linked to a liver specific promoter comprising a portion of the TTR gene promoter instantly claimed. Rather, the Office has combined the general teachings of Snyder regarding the utility of liver-specific promoters with Simonet's teaching regarding the utility of liver-specific promoters in developing transgenic mice to arrive at the instantly claimed invention. Applicants respectfully assert that the mere fact that the prior art references contain elements that can be combined does not render the specific recombinant vector currently claimed obvious. The prior are must not only provide the elements of the invention but also provide a motivation, suggestion, or teaching to make the specific combinations. The Office's general statement that an artisan would have been motivated to make the claimed composition "because factor VIII is expressed in the liver and the promoter TTR used to increase gene expression of a vector in the liver"[1] fails to set forth the specific motivation required to support a prima facie case of obviousness.

Furthermore, the instantly claimed combination requires a particular combination of a B-domain deleted human Factor VIII protein operably linked to a portion of the TTR gene promoter, which Applicants surprisingly discovered yielded high levels of transgene expression. The Office has not provided, nor have Applicants found in the cited references, a teaching or suggestion about the desirability of making the specific, successful combination discovered by Applicants. In fact, the cited references demonstrate that the Office has used impermissible hindsight reconstruction to arrive at the instant invention. Although Synder et al. provides a list of liver-specific promoters, the TTR promoter is notably absent from the list. The Office finds the TTR promoter element in Simonet, a reference whose field relates to "recombinant DNA technology, especially to nucleic acid sequences useful for constructing a transgenic mammal"[2]. Applicants assert that the Office has relied on the instant specification to provide a blueprint to combine the cited references rather than on an objective, permissible motivation to combine.

In addition, the artisan must have had a reasonable expectation of success in making the instant combination; the expectation must be found in the prior art. The Office has not pointed to in the prior art, or even discussed, an expectation of success with respect to the instantly claimed combination. Applicants assert that this expectation is required in a prima facie case of obviousness. Further, Applicants assert that this expectation of success is only provided by the disclosures in the instant

[1] See the Office Action mailed July 19, 2006 at page 5-6.

specification. No information regarding gene expression with respect to constructs comprising the TTR promoter can be identified by Applicants in either Snyder et al. or Simonet.

Therefore, the Office has not provided a motivation to combine the cited references to arrive at the instantly claimed recombinant vector. Nor has the Office provided a reasonable expectation of success with such a construct. In light of the above arguments, Applicants respectfully assert that the Office has not set forth a prima facie case of obviousness for the instant claims. Withdrawal of the rejection is therefore requested.

B) Claims 1, 6, 7, and 8 stand rejected under 35 U.S.C. § 103(a) as being allegedly unpatentable over Snyder et al. (US 2002/0155580) taken with Almstedt (WO 91/09122). In particular, the Office has concluded that it would have been obvious to a person of ordinary skill in the art to make a composition comprising a recombinant AAV comprising a nucleotide sequence encoding a B-domain deleted human Factor VIII protein, wherein said nucleotide sequence further encodes a junction that operably links said heavy and light chain of Factor VIII. Applicants respectfully traverse.

A prima facie case of obviousness requires, in part, that the prior art references teach or suggest all claim limitations. The cited prior art does not teach or suggest the use of a portion of the TTR gene promoter as required by the instant claims. Absent this element in the prior art, the Office has failed to establish a prima facie case of obviousness for claims 1, 6, 7 and 8. Withdrawal of the rejection is therefore requested.

V. Claim rejections under the judicially created doctrine of obviousness-type double-patenting

A) Claims 1-3 and 6-11 stand rejected under the judicially created doctrine of obviousness-type double patenting as being allegedly unpatentable over claims 1-25 of U.S. Patent No. 6,200,560. Applicants respectfully request that the filing of a terminal disclaimer be postponed until allowable subject matter has been identified.

B) A) Claims 1-3 and 6-11 stand rejected under the judicially created doctrine of obviousness-type double patenting as being allegedly unpatentable over claims 1-25 of U.S. Patent No. 6,221,349. Applicants respectfully request that the filing of a terminal disclaimer be postponed until allowable subject matter has been identified.

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[2] Simonet at column 1, lines 1-12.

C) A) Claims 1-3 and 6-11 stand provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being allegedly unpatentable over claims 1-14 of co-pending U.S. Patent Application No. 10/293,400. Applicants respectfully request that the filing of a terminal disclaimer be postponed until allowable subject matter has been identified.

VI. Conclusion

No fee is deemed necessary in connection with the filing of this communication. However, if any fee is required, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 07-1074.

Respectfully submitted,

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Date

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